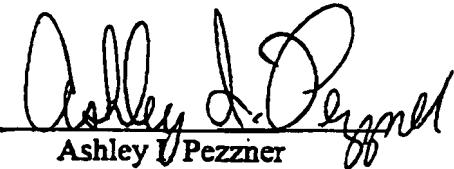


REMARKS

The applicants have added 6 claims and cancelled 6 claims. The applicants authorize the PTO to charge to Deposit Account No. 03-2775 for the fee for the extra independent claim over three. If there are any additional fees due in connection with the filing of this amendment, the applicants authorize the PTO to charge to Deposit Account No. 03-2775. A prompt and favorable action is solicited.

Respectfully submitted,

CONNOLLY BOVE LODGE & HUTZ LLP

By 
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13/Jan/01
DNC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: ELLEN M. DOBRUSIN, ET AL. : EXAMINER: T. TRUONG
SERIAL NO. 09/623,737 : ART UNIT: 1624
FILED: SEPTEMBER 7, 2000 : PAPER NO.
FOR: BICYCLIC PYRIMIDINES AND :
BICYCLIC 3,4-DIHYDROPRIMIDINES :
AS INHIBITORS OF CELLULAR :
PROLIFERATION :
:

Commissioner for Patents
Washington, D.C. 20231

AMENDMENT

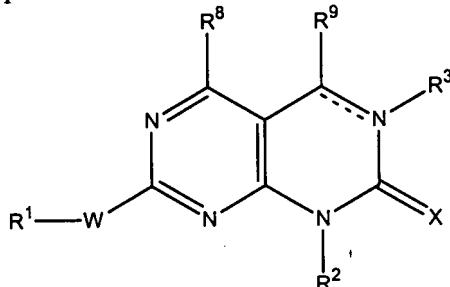
Dear Sir:

Please amend the above-identified application as follows:

In the Claims:

Please amend claims 54, 56 and 60 as follows:

54. (Amended) A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

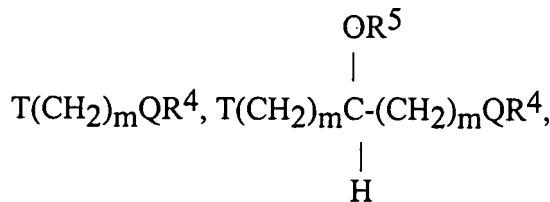
the dotted line represents an optional double bond;

W is NH, S, SO, or SO₂;

X is either O, S, or NR¹⁰;

R¹, R², and R¹⁰ are independently selected from the group consisting of H, (CH₂)_nAr, COR⁴, (CH₂)_nheteroaryl, (CH₂)_nheterocyclyl, C₁-C₁₀ alkyl, C₃-C₁₀

cycloalkyl, C₂-C₁₀ alkenyl, and C₂-C₁₀ alkynyl, wherein n is 0, 1, 2, or 3, and the (CH₂)_nAr, (CH₂)_nheteroaryl, alkyl, cycloalkyl, alkenyl, and alkynyl groups are optionally substituted by up to 5 groups selected from NR⁴R⁵, N^{+(O)}R⁴R⁵, N^{+(O)}R⁴R⁵R⁶Y⁻, alkyl, phenyl, substituted phenyl, (CH₂)_nheteroaryl, hydroxy, alkoxy, phenoxy, thiol, thioalkyl, halo, COR⁴, CO₂R⁴, CONR⁴R⁵, SO₂NR⁴R⁵, SO₃R⁴, PO₃R⁴, aldehyde, nitrile, nitro, heteroaryloxy,



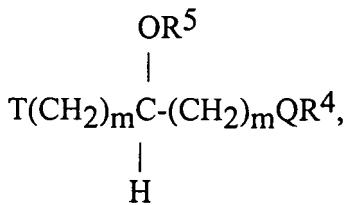
C(O)T(CH₂)_mQR⁴, NHC(O)T(CH₂)_mQR⁴, T(CH₂)_mC(O)NR⁴NR⁵, [or] and T(CH₂)_mCO₂R⁴ wherein each m is independently 1-6, T is O, S, NR⁴, N^{+(O)}R⁴, N^{+(O)}R⁴R⁶Y⁻, or CR⁴R⁵, and Q is O, S, NR⁵, N^{+(O)}R⁵ or N^{+(O)}R⁵R⁶Y⁻;

and additionally alkyl, alkenyl and alkynyl can be further substituted with one to three cycloalkyl groups,

when the dotted line is present, R³ is absent;

otherwise R³ has the meanings of R², wherein R² is as defined above, as well as OH, NR⁴R⁵, COOR⁴, OR⁴, CONR⁴R⁵, SO₂NR⁴R⁵, SO₃R⁴, PO₃R⁴,

T(CH₂)_mQR⁴, or



wherein T and Q are as defined above;

R⁴ and R⁵ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, substituted alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, N(C₁-C₆alkyl)₁ or 2, (CH₂)_nAr, C₃-C₁₀ cycloalkyl, heterocyclyl, and heteroaryl, or R⁴ and R⁵ together with the nitrogen to which they are attached optionally form a ring having 3 to 7 carbon atoms and said ring optionally contains 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur;

when R⁴ and R⁵ together with the nitrogen to which they are attached form a ring, the said ring is optionally substituted by 1 to 3 groups selected from OH,

OR⁴, NR⁴R⁵, (CH₂)_mOR⁴, (CH₂)_mNR⁴R⁵, T-(CH₂)_mQR₄,
CO-T-(CH₂)_mQR⁴, NH(CO)T(CH₂)_mQR⁴, T-(CH₂)_mCO₂R⁴, [or] and
T(CH₂)_mCONR⁴R⁵;

R⁶ is alkyl;

R⁸ and R⁹ independently are H, NR⁴R⁵, N^{+(O)}R⁴R⁵, N⁺R⁴R⁵R⁶Y⁻, COR⁴,
CO₂R⁴, CONR⁴R⁵, SO₂NR⁴R⁵, SO₃R⁴, PO₃R⁴, CN or nitro;

when the dotted line is absent, R⁹ can additionally
be = NOH ,

= NOalkyl , =NOalkenyl, =NOalkynyl or =NOcycloalkyl;
and

Y is a halo counter-ion;

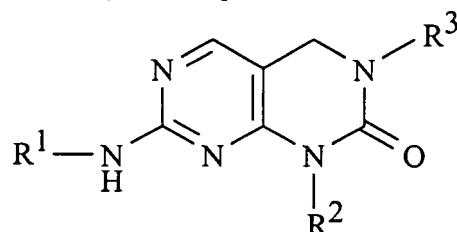
with the proviso that: (a) when R⁸ and R⁹ are both hydrogen, W is NH, R¹ is hydrogen
and X is NR¹⁰, then R¹⁰ is neither unsubstituted (C₁-C₁₀) alkyl, unsubstituted [(C₁-C₁₀)]
(C₂-C₁₀) alkenyl nor unsubstituted [(C₁-C₁₀)] (C₂-C₁₀) alkynyl;

(b) when R⁸ or R⁹ is NR⁴R⁵, N^{+(O)}R⁴R⁵, or N⁺R⁴R⁵R⁶Y⁻, then one or more of R⁴, R⁵ and
R⁶ must be, independent of the nitrogen to which said one or more R⁴, R⁵ and R⁶ are
attached, heterocyclic or heteroaryl; and

(c) when R⁸ or R⁹ is COR⁴, CO₂R⁴, CONR⁴R⁵, SO₂NR⁴R⁵, SO₃R⁴ or PO₃R⁴, then one or
more of R⁴, R⁵ and R⁶ must be, independent of the nitrogen to which said one or more R⁴,
R⁵ and R⁶ are attached, (CH₂)_naryl wherein n is zero, 1, 2 or 3, heterocyclic or heteroaryl;

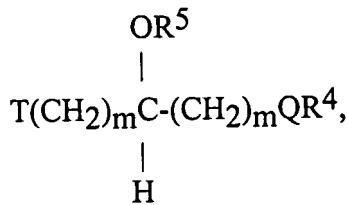
(d) when X is S and W is NH, then at least one of [R1, R2, R3, R8 and R9] R¹, R², R³, R⁸
and R⁹ is other than H or C₁-C₃ alkyl.

56. (Amended) A compound of Claim 55 having the formula

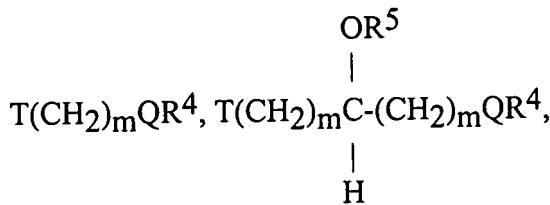


[wherein:

R^1 and R^2 independently are hydrogen, C₁-C₁₀ alkyl, $(CH_2)_nAr$, $(CH_2)_nheteroaryl$, C₃-C₁₀ cycloalkyl, or $(CH_2)_nheterocycl$, wherein n is 0, 1, 2 or 3, and the $(CH_2)_nAr$, $(CH_2)_nheteroaryl$, alkyl, cycloalkyl and $(CH_2)_nheterocycl$ groups are optionally substituted by up to 5 groups selected from NR^4R^5 , $N^+(O)R^4R^5$, $N^+R^4R^5R^6Y^-$, alkyl, phenyl, substituted phenyl, $(CH_2)_nheteroaryl$, hydroxy, alkoxy, phenoxy, thiol, thioalkyl, halo, COR^4 , CO_2R^4 , $CONR^4R^5$, $SO_2NR^4R^5$, SO_3R^4 , PO_3R^4 , aldehyde, nitrile, nitro, heteroaryloxy, $T(CH_2)_mQR^4$,



$C(O)T(CH_2)_mQR^4$, $NHC(O)T(CH_2)_mQR^4$, $T(CH_2)_mC(O)NR^4NR^5$, or $T(CH_2)_mCO_2R^4$ wherein each m is independently 1-6, T is O, S, NR^4 , $N^+(O)R^4$, $N^+R^4R^6Y^-$, or CR^4R^5 , and Q is O, S, NR^5 , $N^+(O)R^5$, or $N^+R^5R^6Y^-$; R^3 has the meanings of R^2 , wherein R^2 is as defined above, as well as OH, NR^4R^5 , $COOR^4$, OR^4 , $CONR^4R^5$, $SO_2NR^4R^5$, SO_3R^4 , PO_3R^4 ,



wherein T and Q are as defined above;

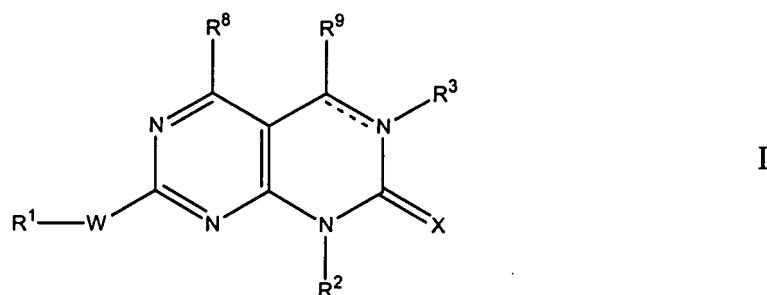
R^4 and R^5 are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, substituted alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, $N(C_1-C_6alkyl)_1$ or 2, $(CH_2)_nAr$, C₃-C₁₀ cycloalkyl, heterocycl, and heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached optionally form a ring having 3 to 7 carbon atoms and said ring optionally contains 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur;

when R^4 and R^5 together with the nitrogen to which they are attached form a ring, the said ring is optionally substituted by 1 to 3 groups selected from OH, OR^4 , NR^4R^5 , $(CH_2)_mOR^4$, $(CH_2)_mNR^4R^5$, $T-(CH_2)_mQR^4$, $CO-T-(CH_2)_mQR^4$, $NH(CO)T(CH_2)_mQR^4$, $T-(CH_2)_mCO_2R^4$, or $T(CH_2)_mCONR^4R^5$;

R^6 is alkyl; and

Y is a halo counter-ion].

58. (Amended) A pharmaceutical formulation comprising a compound of [compound of] Formula I



or a pharmaceutically acceptable salt thereof,
wherein:

the dotted line represents an optional double bond;
 W is NH, S, or SO_2 ;

X is either O, S, or NR^{10} ;

R^1 , R^2 , and R^{10} are independently selected from the group consisting of H, $(CH_2)_nAr$, COR^4 , $(CH_2)_nheteroaryl$, $(CH_2)_nheterocycl$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein n is 0, 1, 2, or 3, and the $(CH_2)_nAr$, $(CH_2)_nheteroaryl$, alkyl, cycloalkyl, alkenyl, and alkynyl groups are optionally substituted by up to 5 groups selected from NR^4R^5 , $N^+(O)R^4R^5$, $N^+R^4R^5R^6Y^-$, alkyl, phenyl, substituted phenyl, $(CH_2)_nheteroaryl$, hydroxy, alkoxy, phenoxy, thiol, thioalkyl, halo, COR^4 , CO_2R^4 , $CONR^4R^5$, $SO_2NR^4R^5$, SO_3R^4 , PO_3R^4 , aldehyde, nitrile, nitro,

heteroaryloxy,
 $T(CH_2)_mQR^4$,

OR^5

|

$T(CH_2)_m C-(CH_2)_m QR^4$,



$C(O)T(CH_2)_m QR^4$, $NHC(O)T(CH_2)_m QR^4$, $T(CH_2)_m C(O)NR^4NR^5$, [or] and
 $T(CH_2)_m CO_2R^4$ wherein each m is independently 1-6, T is O, S, NR^4 ,
 $N^+(O)R^4$, $N^+R^4R^6Y^-$, or CR^4R^5 , and Q is O, S, NR^5 , $N^+(O)R^5$ or $N^+R^5R^6Y^-$;

and additionally alkyl, alkenyl and alkynyl can be further substituted with one to three cycloalkyl groups,

when the dotted line is present, R^3 is absent;
otherwise R^3 has the meanings of R^2 , wherein R^2 is as defined above, as well as
 OH , NR^4R^5 , $COOR^4$, OR^4 , $CONR^4R^5$, $SO_2NR^4R^5$, SO_3R^4 , PO_3R^4 ,

OR^5



$T(CH_2)_m QR^4$, or $T(CH_2)_m C-(CH_2)_m QR^4$,



wherein T and Q are as defined above;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, substituted alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $N(C_1-C_6alkyl)_1$ or 2 , $(CH_2)_n Ar$, C_3-C_{10} cycloalkyl, heterocyclyl, and heteroaryl, or R^4 and R^5 together with the nitrogen to which they are attached optionally form a ring having 3 to 7 carbon atoms and said ring optionally contains 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, oxygen, and sulfur;

when R^4 and R^5 together with the nitrogen to which they are attached form a ring, the said ring is optionally substituted by 1 to 3 groups selected from OH , OR^4 , NR^4R^5 , $(CH_2)_m OR^4$, $(CH_2)_m NR^4R^5$, $T-(CH_2)_m QR_4$, $CO-T-(CH_2)_m QR^4$, $NH(CO)T(CH_2)_m QR^4$, $T-(CH_2)_m CO_2R^4$, [or] and
 $T(CH_2)_m CONR^4R^5$;

R^6 is alkyl;

R⁸ and R⁹ independently are H, NR⁴R⁵, N^{+(O)}R⁴R⁵, N⁺R⁴R⁵R⁶Y⁻, COR⁴, CO₂R⁴, CONR⁴R⁵, SO₂NR⁴R⁵, SO₃R⁴, PO₃R⁴, CN or nitro;

when the dotted line is absent, R⁹ can additionally be = NOH,

= NOalkyl, =NOalkenyl, =NOalkynyl or =NOcycloalkyl;
and

Y is a halo counter-ion;

with the proviso that: (a) when R⁸ and R⁹ are both hydrogen, W is NH, R¹ is hydrogen and X is NR¹⁰, then R¹⁰ is neither unsubstituted (C₁-C₁₀) alkyl, unsubstituted [(C₁-C₁₀)] (C₂-C₁₀) alkenyl nor unsubstituted [(C₁-C₁₀)] (C₂-C₁₀) alkynyl; and

(b) when R⁸ or R⁹ is NR⁴R⁵, N^{+(O)}R⁴R⁵, N⁺R⁴R⁵R⁶Y⁻, COR⁴, CO₂R⁴, CONR⁴R⁵, SO₂NR⁴R⁵, SO₃R⁴ or PO₃R⁴, then one or more of R⁴, R⁵ and R⁶ must be, independent of the nitrogen to which said one or more of R⁴, R⁵ and R⁶ is attached, (CH₂)_naryl wherein n is zero, 1, 2, or 3, heterocyclic or heteroaryl;

(c) when X is S and W is NH, then at least one of [R1, R2, R3, R8 and R9] R¹, R², R³, R⁸ and R⁹ is other than H or C₁-C₃ alkyl;

in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

The terms bracketed are canceled from the claims and the terms underlined are added to the claims. See Appendix 1 for a clean copy of the claims.

REMARKS

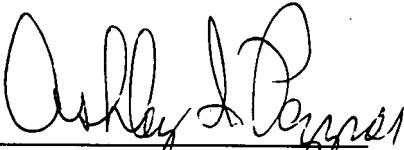
The applicants have corrected clerical errors with respect to claims 54, 56 and 58.

If there are any additional fees due in connection with the filing of this amendment, the applicants authorize the PTO to charge to Deposit Account No. 03-2775.

A prompt and favorable action is solicited.

Respectfully submitted,

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